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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/511,657	04/18/2005	Karina Drumm	129402.00201	9864

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EXAMINER	
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ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/511,657	DRUMM ET AL.	
	Examiner	Art Unit	
	Louis Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 April 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,5,16,94,95,97 and 98* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,5,16,94,95,97 and 98* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/15/2010 has been entered.

Status

Applicant's amendment to the claims filed 4/15/2010 is acknowledged. With entry of the amendment, claims 1, 4, 5, 16, 94, 95, 97, and 98 are pending and examined herein.

Applicant's response filed 4/15/2010 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 2/16/2010 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

Domestic and Foreign Priority

The previous Action explained that written description support is not found in either of the domestic or foreign priority documents for the claimed invention. In particular written description and/or enabling support is not found in Provisional Application 60/431173 or Foreign Priority Application EP02008761.5 for a method of treating disorders related to angiogenesis, neovascularization, the neurosensory retina, or choroid, or any combination thereof, or for methods of treating wet age-related macular degeneration (AMD), diabetic retinopathy, autosomal recessive retinitis pigmentosa, or congenital stationary night blindness by

administration of dsRNAs. Further, no support is found in either of the prior filed applications for methods of treatment further comprising diagnosing a subject with a disorder or predisposition to a disorder of the eye, or isolating the target gene.

To be entitled to the benefits of 35 U.S.C. 119(e), the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

Thus, for purposes of this examination, the earliest effective filing date of claims 1, 4, 5, 16, 94, 95, 97, and 98 is considered to be that of PCT/EP03/04003, filed 4/16/03.

Claim Rejections - 35 USC § 112, first paragraph (Enablement)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4, 5, 16, 94, 95, 97, and 98 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in a determination of lack of enablement include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

The Federal Circuit has repeatedly held that "the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation'." *In re Wright,* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure).

Claim 1 is representative of the method now claimed and reads as follows:

A method for the treatment of autosomal recessive retinitis pigmentosa or congenital stationary night blindness comprising: administering to a subject a therapeutically effective amount of a composition comprising a dsRNA between 21 and 23 nucleotides in length and a carrier, said dsRNA having a nucleotide sequence corresponding to mRNA of a target gene expressed in the eye; said administering of the composition occurring outside the blood-retina barrier, and said composition inhibiting the target gene by RNA interference inside the eye.

The instant application as filed is not considered to reasonably enable one of skill at the time of filing to practice the methods now claimed for treating autosomal recessive retinitis pigmentosa or congenital stationary night blindness by RNA interference (i.e., inhibition) of a target gene without resorting to substantial *de novo* trial and error experimentation and with no assurance of every reaching a successful conclusion, since there is no evidence remotely connecting the treatment of autosomal recessive retinitis pigmentosa or congenital stationary night blindness by inhibiting the expression of any gene and no direction or guidance as to how to achieve the claimed effects other than a general invitation to try. To be sure, the instant application provides no description of any specific interfering RNAs that should be used in the claimed treatment methods, nor any specific guidance as to how to obtain or identify such therapeutically effective interfering RNAs, nor any evidence remotely representative of the method now claimed, and the evidence in the prior art (summarized below) is directly inapposite to the method now claimed.

In particular the instant application does not identify or name a credible target gene or target site in any target gene, wild type or mutant, that should be used for the design of the interfering RNAs required by the methods of the instant claims. A reasonable correlation between the inhibition of any target gene and the treatment of autosomal recessive retinitis pigmentosa or congenital stationary night blindness has not been identified or reasonably established by the instant application, and is not readily apparent from the prior art. Thus, the scope of the claims is not commensurate with enabling support provided by the application as filed.

The claims are drawn to methods of treating autosomal recessive retinitis pigmentosa or congenital stationary night blindness in the eye of a subject, comprising administering to a subject a short interfering double stranded RNA corresponding to mRNA of a target gene. A review of the instant application finds little if any guidance supporting the instant methods. Applicant has pointed to paragraph 97 of the published application, stating the paragraph identifies two specific genes that can be targeted in the claimed method. However, this paragraph does nothing more than cite evidence suggesting a correlation of mutations in CNGA1 and hypothesizes an association between mutations in the alpha and/or beta-subunit of rod cGMP phosphodiesterase with retinitis pigmentosa and night blindness. The paragraph in the specification cites a report by Dryja et al. (Dryja et al. (1995) "Mutations in the gene encoding the alpha subunit of the rod cGMP-gated channel in autosomal recessive retinitis pigmentosa" *PNAS* 92:10177-101) as a reference discussing mutations in CNGA1; however, there is no mention of "CNGA1" in the PNAS paper by Dryja et al. The Dryja et al. paper is entirely devoted to the discussion of mutations in a gene encoding a cGMP-gated channel, and more specifically the α subunit of rod cGMP phodiesterase. It would appear instead that CNGA1 is another name for (is synonymous with) the α subunit of rod cGMP phodiesterase. See Table 2, page 341 in Ramon et al. (2004) "Molecular Biology of Retinitis Pigmentosa: Therapeutic Implications" *Current Pharmacogenomics, 2,* 339-349.

Thus, paragraph 97 hypothesizes a single gene target not two, as asserted by applicant. Further, the report by Dryja et al. clearly states that it is the absence or paucity of functional cGMP-gated cation channels in the plasma membrane that causes retinitis pigmentosa (abstract and see page 10180 bridging to 10181). Dryja et al. explain the mutations identified in patients

with RP, either encode null proteins or proteins that fail to reach the plasma membrane. Accordingly, one of skill would clearly infer that further inhibiting the expression of the functional cGMP phodiesterase gene or the mutant genes was not a treatment option for RP. Rather, it would appear that replacement therapy or therapy designed to correct the mutation was called for. RNA interference is effective for neither of these therapies.

With regard to CNGA1, the art at the time of filing had taught that a mutation in CNGA1 is associated with retinitis pigmentosa (RP). See Trudeau et al. (2002) *Neuron* 34:197-2017. However, the art teaches that in at least one mutant, the CNGA1-RP mutant, the mutation prevents cyclic nucleotide-gated (CNG) channels from being at the surface of rods photoreceptor cells (Trudeau, page 205). Therefore, like rod cGMP phodiesterase, it is the lack of functional channels in the plasma membrane that gives rise to the symptoms of RP. For instance, Trudeau et al. teaches the pathophysiological phenotype of the CNGA1-RP mutant is absence of a CNG current, which is a likely precursor to the degeneration of rod cells that is characteristic of RP (page 198 and see entire report, including results and discussion). The instant application provides no basis and no nexus for understanding how further inhibition with dsRNA of either wild type or mutant CNGA1 will improve vision in an RP patient, as the method does not clearly lead to the increased production of functional channels or correct mutations in existing genes. IN fact, Pardridge (US 20020054902) would appear to suggest the opposite, that a method for treating diseases of the eye, such as retinitis pigmentosa, should or could comprise delivering into the eye genes encoding rod cyclic nucleotide gated channel (CNGA1) and the beta and alpha subuntis of phosphodiesterase (paragraphs 10 and 41).

The specification teaches and the extrinsic literature confirms that SEQ ID NO:3, a 3231-nucleotide DNA, corresponds to human phosphodiesterase 6B, cGMP-specific, rod, beta (PDE6B) mRNA (accession No. NM_000283). The specification teaches and the extrinsic evidence confirms that malfunction of this gene, and more specifically, missense or nonsense mutations in this gene are associated with autosomal recessive retinitis pigmentosa, or congenital stationary night blindness 3 (CSNB3). See, for example, Dryja et al. (1995) "Mutations in the gene encoding the alpha subunit of the rod cGMP-gated channel in autosomal recessive retinitis pigmentosa" *PNAS* 92:10177-10181.

Weber et al. (1991) "Genomic organization and complete sequence of the human gene encoding the 3-subunit of the cGMP phosphodiesterase and its localisation to 4p16.3" *Nucleic Acids Res.* 19:6263-6268 (of record), also taught that the conditions associated with autosomal recessive retinitis pigmentosa (RP) stem from an insufficiency of cGMP phosphodiesterase not an overabundance, stating at page 6267 that:

> Recently, evidence has been provided that the degenerative process in the retinal degeneration (rd) mouse is caused by a defect in the β-subunit of the rod cGMP PDE (8). The rd mouse is considered an animal model for autosomal recessive retinitis pigmentosa (RP) as homozygous mice have been shown to display hereditary progressive degeneration of retinal photoreceptors (36, 37). Retinal degeneration in these mice is preceded by elevated levels of cGMP in the retina as a result of deficient cGMP PDE activity (38, 39).

Hart et al. (2005) "Genotype–Phenotype Correlation of Mouse *Pde6b* Mutations" *Investigative Ophthalmology and Visual Science*. 2005;46:3443-3450 (post filing art) teaches that defects in photoreceptor phosphodiesterase activity caused by mutations in the ß subunit of the rod cGMP-phosphodiesterase (*PDE6B*) gene have been shown to underlie cases of arRP accounting for ~1% to 2% of all cases of RP. It is further taught the product of *Pde6b* contributes

to the heterotetrameric phosphodiesterase complex (PDE, $\alpha\beta\gamma_2$), which regulates cytoplasmic cGMP levels in rod photoreceptors in response to light. On light stimulation, PDE is activated by removal of the γ-inhibitory subunits, resulting in a decrease in cGMP levels and hyperpolarization of the rod cell. In mice with the retinal degeneration 1 (*rd1*) mutation elevated cGMP levels persist because of a homozygous null mutation in the *Pde6b* gene. This results in permanent opening of cGMP-gated cation channels in the membrane of the rod photoreceptors, allowing an excess of extracellular ions to enter the cell, which ultimately leads to cell death by apoptosis.

Altogether, then, the evidence suggests that further suppressing the expression of PDE, as in the method now claimed, would only further exacerbate the night blindness or retinitis pigmentosa present in the subject. While the application as filed disclosed the putative association between mutant PDE and the conditions recited in the claims, the application provides no credible or specific solution for treating the disease by RNA interference. The application describes no exemplary small interfering RNAs, names no particular target sites, and suggests no viable target gene for treating the conditions named. It is unclear then how one of skill could practice the claimed method to treat congenital autosomal recessive retinitis pigmentosa or congenital stationary night blindness without resorting to *de novo* trial and error research.

In fact studies published prior to and after the filing date of the instant application show that suppressing the expression of rod cGMP phosphodiesterase subunits in animals using either ribozymes or antisense oligonucleotides actually lead to photoreceptor and bipolar cell degeneration, conditions associated with retinitis pigmentosa. Indeed researchers have used

antisense and ribozyme-mediated degradation of the genes encoding either the gamma or alpha subunits of rod cGMP-gated channel protein, a cGMP phosphodiesterase, to produce animal models of human retinitis pigmentosa. See, for example, Liu et al. (2005) "Ribozyme Knockdown of the [gamma]-Subunit of Rod cGMP Phosphodiesterase Alters the ERG and Retinal Morphology in Wild-Type Mice" *Investigative Opthalmology & Visual Science* 46:3836-3844; and Leconte et al. (2000) "Impairment of rod cGMP-gated channel alpha-subunit expression leads to photoreceptor and bipolar cell degeneration" *Invest Ophthalmol Vis Sci*. 2000 Mar;41(3):917-26.

While the prior and post filing art clearly correlates autosomal recessive retinitis pigmentosa with a deficiency of functional cGMP-gated channels or cGMP phosphodiesterase (PDE) likely caused by certain nonsense and missense mutations in the gene, neither the specification nor the prior or post-filing art teaches or suggests any link between inhibiting the expression of PDE6B or its mutant alleles and the treatment of the diseases named in claim 99. There is no evidence in the prior art or the specification of any correlation between reducing the expression of any target gene or variant allele and treatment of retinitis pigmentosa or night blindness. Indeed, the literature teaches that it is not the overexpression of phosphodiesterase or its protein product that leads to RP or any other eye disease but the lack of functional phosphodiesterase protein (i.e., paucity of protein) that may be the cause of RP or night blindness. See, for example, Dryja et al., cited above. Even the name, "autosomal recessive," suggests that RP night blindness disorder associated with phosphodiesterase protein is not the result of the expression of an abnormal dominant protein but the lack of normal protein essential to eye function. Thus, it is unclear, and the specification does not show or explain how the

further repression of phosphodiesterase or, for that matter, any other gene target would improve the vision or visual acuity of any subject, particularly those having autosomal recessive retinitis pigmentosa or congenital stationary night blindness. On the contrary it would appear prima facie the expression of the wild type gene should be enhanced or restored to treat the disease, which is not a method within the scope of what is now claimed.

Furthermore, a review of the specification and the prior art fails to find a single working example showing or adequately representing that inhibiting the expression of an mRNA encoding wild-type or mutant PDE6B (such as instant SEQ ID NO:3) or any other target gene produces an effect correlative of treatment in any animal suffering from autosomal recessive retinitis pigmentosa or congenital stationary night blindness. Neither the prior art nor the specification establishes any nexus between the inhibition of a target gene and the treatment of each of these diseases. Accordingly, it is reasonable to question the objective truth of the assertions in the claims that the administration of an interfering dsRNA targeting PDE (e.g., SEQ ID NO:3) or any other target gene may be used to treat each of the disorders recited therein. With no examples to draw on and no direction or guidance of any kind in the specification showing how or even whether inhibition of a target gene or any isoform thereof may be used to treat each of these disorders named in claim 1 one of skill would necessarily need to resort to *de novo*, trial and error experimentation to achieve the claimed effects, and with no assurance of ever reaching a successful conclusion. The effects promised by the claims represent hoped-for functions---a starting point for further research, but nothing more. Such research, in the absence of any direction, guidance, or assurance by the specification, is considered to be undue.

Moreover, enabling support in the manner required by 35 USC 112, first paragraph, must be present at the time of filing. To overcome a *prima facie* case of lack of enablement, applicant must demonstrate by argument and/or evidence that the disclosure, as filed, would have enabled the claimed invention for one skilled in the art at the time of filing (MPEP 2164.05 and 2164.05(a)). To date, the only guidance and direction present at the time of filing identified by applicant and the examiner concerns the passage at paragraph 97 of the published application, wherein the mutation or malfuinction two genes are said to be associated with autosomal retinitis. The paragraph reads:

> Hence, in a first set of experiments several nucleic acid molecules could be identified which indeed were known to be involved in autosomal recessive retinitis pigmentosa (ARRP), which inter alia is characterized by the degeneration of retinal photoreceptor cells. For example, nucleic acid molecules could be indentified corresponding to the gene encoding the human cyclic nucleotide gated channel alpha 1 (CNGA1, accession No. NM.sub.--000087; SEQ ID NO: 1 and 2). Mutations in this gene have been described to be involved in autosomal recessive retinitis pigmentosa; see Dryja et al., Proc. Nat. Acad. Sci. USA 92 (1995), 10177-10181. In another experiment, nucleic acid molecules corresponding to the human gene encoding the beta-subunit of rod cGMP phosphodiesterase (accession No. NM 000283; SEQ ID NO: 3 and 4) have been identified. Malfunction of this gene has also been associated with autosomal recessive retinitis pigmentosa, in particular with congenital stationary night blindness 3, CSNB3. These results confirm that the method of the present invention works.

There is no disclosure of any other gene or genes or particular dsRNA or target site in any gene or any other description of which gene, mutant or wild type, to target with the dsRNA or any other instructions as to how to particularly achieve the treatment effect required by the claims. It is noted the specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991). However, in this case, a review of the prior art fails to find any disclosure supporting the claimed method and only disclosure suggesting that the method as claimed, at least with regard to the inhibition of the

α- or β-subunit of rod cGMP phosphodiesteras, would only exacerbate the conditions recited in the claims, autosomal retinitis or night blindness, or have no effect at all.

It is noted that the claimed methods are not limited to any particular gene target, but include any gene known at the time of filing or yet to be discovered whose disruption by dsRNA would provide for treatment of autosomal recessive RP or night blindness. However, neither the prior art nor the specification identifies a credible target or shows or suggests how to practice the method with any other gene target. And any target discovered after the filing date and unknown at the time of filing that may provide for the effect by dsRNA can not properly be relied on for the support if such knowledge was not in the prior art or the specification. "…[A] patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion" (*Brenner, Comr. Pats. v. Manson*, 148 USPQ 689 (U.S. 1966)).

Thus, considering the breadth of the claims, the state of the art at the time of filing, the level of unpredictability in the art, and the limited guidance and working examples provided by the instant application, the Examiner submits that the skilled artisan would be required to conduct undue, trial and error experimentation to use the claimed invention commensurate with the claims scope.

Accordingly, the instant claims are rejected for failing to comply with the enablement requirement.

Response to Arguments

Applicant's arguments filed 4/15/2010 traversing the enablement rejection have been considered but are not persuasive. Applicant argues the Office has not met its burden to show the presently claimed method is not enabled. Specifically, Applicant alleges the Office provides no

evidence or reasoning to justify the rejection. The Examiner respectfully disagrees. Several specific publications have been cited and adequate reasoning provided to question the objective truth of the statement in the claims. Applicant cites two specific genes that can be targeted by the instant method. See paragraph 97. The instant application provides no guidance or direction in support of the claimed method beyond that shown in the prior art. There are no siRNAs described and no evidence to show reduction of any particular target gene will treat RP or night blindness. A review of the prior art suggests that, at least with regard to the two genes cited in the application, treatment of the diseases recited in the claims would require replacing these genes not further depleting them, and all the mutations identified by the prior art are ones that lead to loss of functional protein not the production of deleterious protein. For example, Pardridge (US 20020054902) suggests methods for treating diseases of the eye, including retinitis pigmentosa, comprising delivering into the eye genes encoding rod cyclic nucleotide gated channel (CNGA1) and the beta and alpha subuntis of phosphodiesterase (paragraphs 10 and 41).

Apart from the bare statement in the application that mutations of certain genes have been correlated with the eye diseases, Applicant adduces no countervailing evidence to rebut the prima facie case of non-enablement set forth by the Office.

MPEP 2164.04 states in order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). The language should focus on those factors, reasons, and evidence that lead the examiner to conclude that the specification fails to teach how to make and use the claimed invention without undue

experimentation, or that the scope of any enablement provided to one skilled in the art is not commensurate with the scope of protection sought by the claims. This can be done by making specific findings of fact, supported by the evidence, and then drawing conclusions based on these findings of fact. For example, doubt may arise about enablement because information is missing about one or more essential parts or relationships between parts which one skilled in the art could not develop without undue experimentation. In such a case, the examiner should specifically identify what information is missing and why one skilled in the art could not supply the information without undue experimentation. See MPEP § 2164.06(a). References should be supplied if possible to support a *prima facie* case of lack of enablement, but are not always required. *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). However, specific technical reasons are always required.

The Examiner respectfully refers Applicant to the rejection above and submits he has met his burden in this regard. Applicant points to paragraph 97 and states this section names two specific genes that can be targeted in the instant method to treat RP and night blindness. Neither the application nor the prior art provide any working example or any specific technical guidance or evidence beyond the mere statement in the claims to show or suggest that inhibiting the expression of the wild type or mutant form of these genes, CNGA1 or cGMP PDE, or any other gene, will provide a beneficial effect or improve the vision in any patient. The Examiner recognizes that actual reduction to practice or evidence of operability is not required. However, there is reason to question the operability of the method when a review of the prior art finds only evidence suggestive of a method that is directly opposite to what is now claimed, wherein treating RP or night blindness would appear to require replacing functional genes not further

inhibiting the expression of any gene in the eye. The application only refers to the native mRNA sequences. Inhibiting the expression of the functional native sequences will not treat RP, and the mutant genes generally referred to by the application are not specifically identified, and the prior art shows only that the mutant forms of PDE lead to loss of functional channels and that it is the deficiency in protein that causes disease not the presence of missense or null protein. For example, with regard to phosphodiesterase, the prior art shows that RP and night blindness is caused by the absence or loss of functional cGMP gated channels. While CNGA1 had been generally correlated with RP and night blindness, the prior art suggested delivering constructs encoding CNGA1 to treat the eye disease not inhibiting CNGA1. See, for example, Pardridge above.

Accordingly, the claims stand rejected for lack of enablement because one of skill would need to resort to *de novo* trial and error experimentation to practice the instant method with no reasonable expectation of ever reaching a successful conclusion. Such experimentation in the absence of any direction is considered undue. The specification provides no credible mRNA target and describes no dsRNA(s) capable of producing the effects asserted by the claims.

It is noted that that Lewin et al. had reported a ribozyme treatment that slowed the rate of photoreceptor degeneration in a transgenic rat model of autosomal dominant retinitis pigmentosa containing a dominant rod opsin mutation (proline-to-histidine change at position 23). However, the instant claims do not appear to embrace treatment of autosomal dominant RP, but are limited only to those methods involving genes and gene variants responsible for autosomal recessive RP. See Lewin et al. (1998) "Ribozyme rescue of photoreceptor cells in a transgenic rat model of autosomal dominant retinitis pigmentosa" *Nature Med.* Aug;4(8):967-71. Moreover, if the claims

were considered to embrace adRP as well arRP, or if the claims were amended to specifically embrace adRP, the Examiner would be required to consider the relevance of the Lewin et al. disclosure to the patentability of the claims under 35 USC 103.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis Wollenberger whose telephone number is (571)272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Louis Wollenberger/
Primary Examiner, Art Unit 1635
July 21, 2010